IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVOZYMES A/S, Plaintiff v. GENENCOR INTERNATIONAL, INC., and ENZYME DEVELOPMENT CORPORATION Defendants	C.A. No. 05-160-KAJ

PLAINTIFF NOVOZYMES' POST-TRIAL OPENING BRIEF

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I. STATEMENT OF FACTS

This patent infringement case was brought by plaintiff Novozymes A/S ("Novozymes") on March 15, 2005. **A1501.**[1] The defendants are Genencor International, Inc. ("Genencor") and Enzyme Development Corporation ("EDC"); collectively "Genencor." They infringe Novozymes' U.S. Patent No. 6,867,031 for "Amylase Variants" ("the '031 Patent"), by their manufacture, use and sale of an alpha-amylase product called Spezyme® Ethyl. A bench trial was held on March 6-9, 2006 on issues of infringement, validity and unenforceability. This is Novozymes' Post-Trial Brief.

A. Background

1. The Parties and Their Dispute

Novozymes is the world's largest producer of industrial enzymes. **A5016:24-25**. This has led to many patentable inventions, including the alpha-amylase variants of the '031 patent. These variants are thermostable; they keep working after long exposure to high temperature. This breakthrough was important for industry, and particularly for processes that use the enzymes to liquefy starch, *e.g.*, to make fuel ethanol. **TE-100, A7009 at 3:11-24; A5025:3-5026:4.**

Genencor is accused of infringing claims 1, 3 and 5 of U.S. Patent No. 6,867,031 (the '031 patent). As shown at trial, Genencor's Spezyme® Ethyl product is an alpha-amylase variant having all of the required features of these '031 patent claims.

Genencor introduced Spezyme Ethyl in April of 2004 to compete with Novozymes' alpha-amylase. **A1006 ¶V-X.** Genencor's other alpha-amylases, such as GZYME G997 and Spezyme Fred, were not suitable for demanding industrial conditions. **A5032:12-5039:11; A5046:14-21, A5048:13-5049:24.** Genencor's effort to engineer an alternative was unsuccessful. ***Id.*** Frustrated, Genencor acquired a competitor, EBS, and its thermostable alpha-amylase, "EBS2." ***Id.*** Genencor chose to market EBS2 as Spezyme Ethyl, even though it knew about dominating claims in

[1] Citations are to numbered pages of the trial record, presented as an accompanying Appendix. Line numbers are indicated by a colon. *E.g.*, **A5017:5-9** means lines 5-9 of page **A5017**. Emphases in quotations are added, unless otherwise indicated.

Novozymes' '031 patent application. **A5014:4-14; A5663:16-5664:21.** Novozymes also gave Genencor a copy of the allowed claims in September 2004 to no avail. ***Id.*** Genencor's sales continued. **A1006, ¶ Y.** This suit began on March 15, 2005 (**A1501**), the day the '031 patent issued. **TE-100, A7002.**

2. The Technology of the '031 Patent -- Protein Engineering

The '031 Patent is concerned with alpha-amylase enzymes, which catalyze a biochemical reaction that degrades starches into smaller molecules. **A1003 ¶E.** These enzymes are highly thermostable, engineered variants of alpha-amylases that originate from *Bacillus* bacteria. **TE-100, A7040** (claims 1-5); **A5022:16-5027:14.**

All proteins, including alpha-amylases, are chains of amino acids joined by chemical bonds. There are 20 different amino acids, "residues," and each protein has many of them assembled in a unique sequence, or primary structure. **A1004, ¶I; A5019:4-13.** A protein's three-dimensional structure is determined by the amino acid chain, which "folds" into a working shape under suitable conditions. **A5021:1-7; A5687:11-19.** A protein sequence can be written in consecutive order using one-letter abbreviations for each residue, with a number for each position in the sequence. **A1004, ¶J-L.** For example, R178 indicates Arginine at position 178 of the sequence. Sequences are read from an "N-terminus" on the left to a "C-terminus" on the right. ***Id.***

Two or more sequences can be compared by "aligning" them with each other to produce an optimal juxtaposition showing amino acids that are common to both proteins. **A1005, ¶N.** The percentage of identical amino acid matches in two aligned sequences can be determined and reported as the percent identity (a/k/a "homology") of the two proteins. **Id., ¶O.** When two aligned proteins have different lengths, their consecutive numbered positions from N to C termini may not coincide because of gaps where one sequence has no matching residues in the other. Thus, a reference sequence can be used for numbering all of the sequences in an alignment. **A5639:3-18**

The patented alpha-amylases are engineered. A protein engineer works to "change the amino-acid sequence of the enzyme in order to make it function better in various industrial

processes" (**A5018:14-19**), *e.g.*, at high temperature (**A5018:20-5019:1**). *See also* **A5017:5-9; A5136:16-21**. These changes include insertions, deletions, and substitutions of amino acids in a protein. **TE-100, A7009 at 3:59-65**; **A5023:9-13**. This can be done by modifying the DNA of the gene responsible for producing the protein. **A5140:4-25; A5204:3-9**. Often, the starting point is an unmodified or naturally-occurring ("wild-type") protein. **A5021:2-4.** Variant proteins are made by altering the DNA of a gene for that protein to make a variant gene that produces the variant protein. **A5140:19-25; A5204:1-11**. Thus, the amino acid sequence of the variant is altered with respect to the sequence of the unmodified protein, which can be called a "parent." **A5138:19-5139:9**.

The amino acid sequence of a protein can be determined from a sample of the protein by well-known methods. **A5057:14-5059:14** A theoretical sequence can also be predicted from the DNA of a gene for the protein according to the genetic code. **A5140:4-25; A5204:1-11** However, the protein may not be rendered as predicted. **A5228:11-14; A5181:1-6**. Some parts of a gene are not translated or are used to control protein production. **A5207:19-5209:6; A5504:13-15.** A protein translated from DNA may be further processed, *e.g.*, by cleaving amino acids from one or both ends. Thus, the gene may encode a "pre-protein" (**A5208:17-21**), followed by "post-translational modification" to yield a final product. **A5204:18-5205:3**. Thus, the actual sequence may not be the sequence predicted from DNA. **A5228:11-14; A5181:1-6**.

3. Alpha-Amylase Enzymes

Novozymes' '031 patent is concerned with variants of enzymes called alpha-amylases; they have alpha-amylase activity. **A1003; TE-101, A7001 *et seq.*; A5022:6-5023:5**. The "activity" of an enzyme is a measure of its ability to catalyze a specific biochemical reaction under given conditions. Enzymatic activity decreases over time, and the remaining activity after a retention time can be called "residual activity." **A5052:23-5053:12; A5745:10-5746:9.** Measurements of activity (assays) are often conducted under stressful conditions, such as elevated temperature. ***Id.***

Alpha-amylases catalyze a reaction that degrades starch into smaller molecules. Starch is made of many glucose sugar molecules joined together by chemical bonds. **A1003**. They are

produced by many organisms including various species of the bacteria *Bacillus*. The patent focuses on thermostable *B. stearothermophilus* alpha-amylase variants. **TE-100, A7009 at 3:10-4:35**.

B. The Novozymes '031 Patent

The Novozymes '031 patent "relates to a-amylase variants having improved properties relative to the parent enzyme (*e.g.*, improved thermal and/or oxidation stability and/or reduced calcium ion dependency)." ***Id.*** **A7008-7009 at 1:21-24; 2:61-3:7, 3:65-4:35**. A goal of the work "was to improve, if possible, the stability of, inter alia, particular a-amylases which are obtainable from *Bacillus* strains." ***Id.*** **7009 at 3:10-14**. Improved thermostability is particularly important for alpha-amylases that are used for industrial starch liquefaction, *e.g.*, for fuel ethanol. ***Id.*** **7008 at 1:35-3; A1003**. One way to evaluate thermostability is to conduct a thermal inactivation assay, *e.g.*, to determine the time by which an enzyme loses half of its activity under given conditions, including temperature. This is called the half-life of thermal deactivation, or just "half-life." **A5746:18-25**.

The patented variants can be made by genetic engineering. **TE-100, A7008 at 1:26-28, A7010 at 5:5-48**. These techniques are used to modify one or more amino acids of an alpha-amylase, by deletion, substitution, or insertion, *e.g.*, to improve thermostability. ***Id.*****, A7012 at 9:48-10:3.** "Particularly interesting pairwise deletions of this type are . . . R179*+G180* . . . (SEQ. ID No. 3)" ***Id.***. The '031 claims focus on these deletions, from among other modifications that are also disclosed. ***Id.*** **A7040**. The same 179,180 deletion is important for reduced calcium dependency. ***Id.*** **A7012 at 10:40-56, A7013 at 11:41-65**. These variants exhibit a satisfactory activity "in the presence of a lower concentration of calcium ion." ***Id***. This is important because other fuel ethanol enzymes used later in the process need low calcium, necessitating calcium removal (at significant effort and cost) if a high-calcium alpha-amylase is used **A5025:21-5026:11.**

1. The '031 Prosecution History and Cited Prior Art

The '031 patent issued from application No. 10/025,648, filed on December 19, 2001, ("the '648 application") and published on April 3, 2003. The first-filed U.S. application leading to

the patent was filed on February 5, 1996 and claimed priority to February 3, 1995. **TE-100, A7002.** The '648 application included a Preliminary Amendment (**TE-101, A7045-48**), which, *inter alia*, added claims 30-39 for variant alpha-amylases. ***Id.*** **at A7045-47**. Claim 30 stated (**A7045**):

> [a] variant of a parent alpha-amylase enzyme, wherein said parent alpha-amylase has an amino acid sequence which has at least 80% homology to SEQ. ID NO. 3, and wherein said variant comprises deletions at positions equivalent to positions 179 and 180 in SEQ. ID NO. 3 (using SEQ. ID NO. 3 for numbering).

Other claims specified 85%, 90% or 95% homology. **A7045-46** (claims 31-33). Thus, by December 2001, Novozymes was claiming the invention at issue here.

The United States Patent and Trademark Office ("PTO") issued an Office Action on July 29, 2003. **TE-101, A7619-29**. The claims were rejected as indefinite and for insufficient enablement and description (35 U.S.C. § 112). ***Id.*** **at A7622-27**. They were also rejected as obvious (35 U.S.C. § 103) over Suzuki (**TE-115**) and Bisgärd-Frantzen (**TE-177**). ***Id.*** **at A7627-28; A1007-8**. Novozymes' responded on January 14, 2004. ***Id.*** **at A7633-37**. The claim language was clarified, and cysteine substitutions were added to the 179,180 deletion. ***Id.*** **at A7636**. An Office Action followed on April 6, 2004. ***Id.*** **at A7717-27**. The Examiner found that the specification "is enabling for an alpha-amylase having at least 90% homology to SEQ. ID. NO. 3," but 80% was too broad. ***Id.*** **at A7721**.

On September 3, 2004, Novozymes' attorney Jason Garbell and co-inventor Torben Borchert met with Examiner. Novozymes discussed broader claims and a draft Declaration by Dr. Borchert. ***Id.*** **at A7735, A7798-99; A5013:12-22.** The Declaration was filed on September 7, with new claims 48-52 (now claims 1-5 of the patent). ***Id.*** **at A7733-56; TE-100, A7040**. An Allowance followed on September 21 (***Id.*** **at A7791-97**), stating that the Declaration, "establishes that the claimed variants exhibit unexpectedly large increases in thermostability when compared to the increases in thermostability obtained for the corresponding mutations taught by Suzuki et al. As such the claimed variants are non-obvious over the prior art." ***Id.*** **at A7796**.

2. Other Prior Art: The Machius '95 Reference

Another reference, Machius '95 (**TE-173**), describes secondary structural elements (characteristic shapes) that comprise the three-dimensional structure of a wild-type *B. licheniformis* alpha-amylase ("BLA"). **A5699:17-19.** From this, Machius speculates that Suzuki's double-deletion in *B. amyloliquefaciens* (residues R176 and G177 in BAA) alpha-amylase may be in a "loop" structure, which would be larger by two residues in BAA compared to BLA. Hypothetically, the enlarged loop might indicate why BAN is less stable than BLA. **TE-173, A8384; A5703:6-18,** *see also*, **A6522:19-6523:4**. Other explanations are also considered, all of them inconclusive. **TE-173, A8384; A6522:7-12.**

The crystal structure of Machius '95 had technical problems, and was not actually disclosed.[2] Dr. Machius used a calcium-depleted BLA alpha-amylase that was inactive. **A5729:23-5730:8.** Later work confirmed that BLA structures "exhibit drastically different formations depending on whether the [calcium] metal ions are bound or not." **A5728:4-14** (citing **TE-175, A8397**); **A5704:13-23; TE-175, A8391**. Also, the protein in the 1995 crystal was cleaved near the site corresponding to Suzuki's BAA double-deletion, and Dr. Machius did not have data to resolve this region. **A5701:23-5702:16; A5730:15-21.** These problems made the 1995 structure highly questionable, and undermine any theories to be drawn from the reference. **A5730:22-5731:15; TE524, A8915 ¶ 42.**

Machius merely summarized Suzuki and added some notions about "X-ray determined secondary structure elements of BLA." **TE-173, A8384**. This was "very little more" than was already known about *B. licheniformis* (BLA) alpha-amylase. **A5688:7-12.** There is no structure or data for wild-type BAN or the Suzuki BAN variants. Machius itself noted that theories attempting

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[2] Machius gave a general description of a BLA X-ray crystal structure, using secondary shapes. **TE-173; TE524, A8915 ¶39**. Crystallographers model 3D structure using X,Y,Z coordinates for every atom of a crystallized protein. The coordinates are the structure, and give what scientists hope is a good 3D representation. **A5685:2-12.** The coordinates are not in Machius, and only became public later (**A5718:1-15**), after the critical date for prior art. **A5716:11-5718:23; A5724:25-5725:8; A5725:23-A5727:12; TE-100, A7008 at 1:6-17.**

to explain Suzuki are uncertain, including the loop idea. Such proposals "cannot be judged, because of the lack of the three-dimensional structures of BAA and the [Suzuki] mutants" (**TE-173, A8384**). There is also no structure or data for a *B. stearothermophilus* alpha-amylase or variants. Speculation about "why" Suzuki may have been successful does not add to that success. There is nothing from which to predict the degree of improved thermostability a *B. stearothermophilus* variant would or could achieve. **A6529:17-19; A6519:15-6520:13; A6550:16-19.**

3. Claims 1, 3 and 5 of the '031 Patent

Claims 1, 3 and 5 of the patent are directed to variant alpha-amylases that have a deletion of the amino acids at positions equivalent to 179,180 of SEQ. ID NO. 3 in the patent. **A1005; TE-100, A7040**. Claim 1 compares the amino acid sequence of the variant to the amino acid sequence of its *B. stearothermophilus* parent to determine, the "percent homology" to the parent. **TE-100, A7040 at 65:11-17; A5141:6-20.** Claim 3 compares the amino acid sequence of the variant to the amino acid sequence of SEQ. ID. NO. 3 to determine the "percent homology" to SEQ. ID. NO. 3. **TE-100, A7040 at 65:21-66:12; A5145:5-5146:20**. In claim 5, the 179,180 deletion is the only difference between parent and variant. **TE-100, A7040 at 66:17-20; A5147:4-23**.

A "variant" is the result of the deletion, substitution, or insertion of amino acids relative to a parent alpha-amylase. **TE-100, A7009 at 3:59-67**; *see also* **A5138:23-5139:20**. This is done in order to provide modified properties "relative to the parent enzyme." **TE-100, A7008 at 1:20-25, 2:61-63**. A parent enzyme is improved, 'by judicial modification of one or more amino acid residues in various regions of the amino acid sequence of the parent alpha-amylase." ***Id.*, 7009 at 3:17-25**); *see also* ***id.* at 7010, 5:49-57**. This is the ordinary usage of the term "variant" in protein engineering. **A5138:23-5139:9**; **A5203:2-11**.

The specification teaches that a parent is an antecedent protein that is altered to provide a variant protein. **TE-100, A7008 at 1:21-24** ("variants having improved properties relative to the parent enzyme"), **2:61-65** ("variants which -- relative to their parent alpha-amylase -- possess improved properties"), **3:30-35** (goal is to improve the stability of certain alpha-amylases

obtainable from Bacillus strains), **3:10-14, 18-23**. Non-limiting examples are disclosed (***Id.*** **at A7009, 3:25-42**), and other parents are also suitable. ***Id.*** **at A7011, 7013-14 at 7:52-67, 12:49-52, 13:24-25**. A parent protein is made from a predecessor gene relative to the variant, often a naturally occurring (a/k/a "wild-type") gene; its protein sequence is unaltered. **A5150:13-5151:7; TE-100, A7016 at 17:18-19.** The ordinary meaning of "parent" in protein engineering accords with this usage in the specification. **A5175:6-7; A5203:5-11**.

Claim 1 also provides that the parent is a "*B. stearothermophilus* alpha-amylase" and the resulting variant has "alpha-amylase activity." **TE-100, A7040.** This is the ability to catalyze reactions that break down and liquefy starch. **A1003**. *B. stearothermophilus* is one species of the *Bacillus* genus of bacteria. **A1005**. It is an organism found in soil that produces alpha-amylase. **A5139:23-5140:14**. This alpha-amylase originates from a *B. stearothermophilus* organism; it is produced by a *B. stearothermophilus* alpha-amylase gene. **TE-100, A7011 at 7:32-35; A5140:1-14; A5150:13-25**.

The claim 1 variants have "an amino acid sequence which has at least 95% homology to the parent *B. stearothermophilus* alpha-amylase." **TE-100, A7040.** The meaning of "percent homology" in the context of the invention is as follows (**TE-100, A7009 at 4:36-40**):

> An amino acid sequence is considered to be X % homologous to the parent alpha-amylase if a comparison of the respective amino acid sequences, performed via known algorithms, such as the one described by Lipman and Pearson in Science 227 (1985) p. 1435, reveals an identity of X %.

The patent equates "percent homology" with "percent identity" (***Id.*****; A1005**), and teaches how to make this determination. "The GAP computer program from the GCG package, version 7.3 (June 1993), may suitably be used ..." **TE-100, A7009 at 4:40-45**. The patent also directs the artisan to use alignment algorithms according to Lipman & Pearson. **TE-100, 4:36-40**. However, there is no dispute in this case about the proper alignment of the relevant sequences.

GAP GCG calculates percent identity as a comparison of the number of identical matches between two sequences. "Percent identity takes the sum of all the matching residues where there is

a corresponding part in both sequences." **A5111:2-6; A5110:22-5112:12**. This is a standard percent identity calculation, and answers a routine question in protein engineering: How much of one sequence is present in the other sequence? **A5118:3-10**. The GAP program "leads you to a particular calculation of that percent identity." **A5146:14-5147:1**; **A5141:21-5142:3**.

Each claim 1 variant, compared to its parent, "comprises a deletion of amino acids 179 and 180 using SEQ. ID NO. 3 for numbering." **TE-100, A7040**. SEQ. ID NO. 3 is set forth in the '031 patent. ***Id.* at A7003, Fig. 1, A7030-7032.** It is the sequence for a preferred parent *B. stearothermophilus* alpha-amylase in some of the examples. ***Id.* A5142:5-23**. It is also a reference sequence, used to specify the positions of matching residues in an alignment. **TE-100, A7040.** "[U]sing SEQ. ID. NO. 3 for numbering" means that SEQ. ID. NO. 3 is a reference; it is not claimed as a parent. The positions of amino acids in an alignment are assigned according to equivalent positions (residue numbers) in SEQ. ID. NO. 3. The residues of a parent sequence that align with positions 179,180 of SEQ. ID. NO. 3 are present, but they are not present in the aligned variant. This is customary in the protein engineering field. **A5142:5-A5143:10; A5639:5-18**.

Claim 3 differs by providing a variant alpha-amylase with at least 95% homology to SEQ. ID NO. 3 (not a "parent"). The same 179,180 deletion using SEQ. ID NO. 3 for numbering is claimed, as is alpha-amylase activity. **A7040; A1005**. A "variant alpha-amylase" means that the variant is an altered alpha-amylase, but claim 3 does not require sequence comparison to a parent. Instead, the variant is compared to SEQ. ID. NO. 3. **TE-100, 7040**; **A5145:13-25**. The "percent homology" comparison is also with SEQ. ID NO. 3, not with a parent. **A5146:10-13**.

Claim 5 recites "a variant of a *Bacillus stearothermophilus* alpha-amylase, wherein the alpha-amylase variant consists of a deletion of amino acids 179 and 180, using SEQ. ID NO. 3 for numbering." **TE-100, A7040; A1006**. This means that the only difference between the unmodified *B. stearothermophilus* alpha-amylase and the variant is the 179,180 deletion. **A5147:12-23**.

C. Genencor and the Accused Spezyme Ethyl Product

Genencor stipulates that it began selling Spezyme Ethyl in the U.S. by April of 2004. **A1006.** Spezyme Ethyl is unquestionably an engineered variant of a *B. stearothermophilus* parent and it has alpha-amylase activity. Genencor admits: "The alpha-amylase from which SPEZYME® Ethyl was derived is the alpha-amylase of *Bacillus stearothermophilus* strain ASP154, ATCC deposit no. 39,709. SPEZYME® Ethyl has alpha-amylase activity." **TE-194, A8521**. This same ATCC 39,709 wild-type *B. stearothermophilus* alpha-amylase has also been called GZYME G997 or simply G997. **A5045:16-19; TE-161, A8366**. Spezyme Ethyl is a "variant alpha-amylase" (claim 3); it is a "variant of a *B. stearothermophilus* alpha-amylase" (claim 5); and it is a "variant of a parent *B. stearothermophilus* alpha-amylase" (claim 1).

According to work by Genencor's Judy Chang in 2004, "EBS2 is a recombinant alpha-amylase derived from *Geobacillus stearothermophilus*" (**TE-161, A8365**), a recent name for *B. stearothermophilus*. **A1005**. Spezyme Ethyl was also called EBS2. **A5032:3-8.** According to Genencor, EBS2 [Spezyme Ethyl] "differs from the wild-type stearothermophilus enzyme in two amino acid deletions, the Arginine and Glycine at positions 181 and 182." **TE-161, A8365**. This 181,182 numbering is for alignment with *B. licheniformis* alpha-amylase. ***Id.* at A8365, n.1**. "When aligned against the wild-type *stearothermophilus* alpha-amylase, the amino acids are found at positions 179 and 180." ***Id.***

Thus, Spezyme Ethyl is derived from and is a variant of GZYME G997, a wild-type *B. stearothermophilus* alpha-amylase. **A5039:12-5040:8; A5045:16-19, A5046:10-13, TE-194, A8521, A8525.** GZYME G997 is the parent of Spezyme Ethyl. ***Id.***; **A5148:8-5149:18; A5167:10-21**. The engineered difference between the variant Spezyme Ethyl and the G997 parent is the deletion of the amino acids at positions 179,180. **TE-161, A8365, A8369** (deletions confirmed); **A5162:9-22** (Dr. Arnold); **A5259:23-5260:3; A5260:21-5261:5**. Spezyme Ethyl has the 179,180 double-deletion of claim 1, 3 and 5, and it is the only engineered difference (claim 5).

The 484 amino acid sequence of Spezyme Ethyl is stipulated. **A1006-1007.**

The amino acid sequence of G997 has been determined by Dr. Christian Jorgensen of Novozymes. Dr. Jorgensen regularly analyzes, characterizes and identifies proteins, including determining their sequences and molecular weights. **A5058:5-16**. He has done this for thousands of proteins. **A5060:16-18**; **A5057:14-5058:4; A5058:17-22; A5060:5-15; A5055:5-5056:19**.

Dr. Jorgensen's analysis of G997 (**TE 206, A8537-40; A5065:16-23**) identified a single *B. stearothermophilus* alpha-amylase weighing 58kD. **A5069:18-25; A5070:6-11**. This alpha-amylase was purified and analyzed further. **A5099:13-19**. Mass spectrometry, SDS PAGE, and C-terminal digestion were used. **A5069:9-5071:9; TE206, A8537-8539.2; A5098:12-5099:6.** Dr. Jorgensen determined the 486 amino acid sequence of G997 **TE 199, A8529; A5071:18-21.** Dr. Arnold reviewed Dr. Jorgensen's work and found that he analyzed an authentic G997 protein and correctly determined its sequence. **A5166:25-5169:5.** Dr. Jorgensen repeated his analysis on additional samples of G997. **A1721-25**. He found the identical sequence. ***Compare* TE-199 *and* TE-226**. Genencor has stipulated that the sequence in **TE-226** "is the sole amino acid sequence of the only alpha-amylase determined by Novozymes from its analysis to be present in the samples of GZYME G997 provided by Genencor." **A1721**.

The 484 amino acid sequence of Spezyme Ethyl (**TE-194, A8521-22; TE-125**) can be directly compared to the 486 amino acid sequence of G997 determined by Dr. Jorgensen. (**TE-199, A8529; TE-124; TE-226**). These two sequences are identical, except that the two amino acids at positions 179,180 of G997 are deleted in Spezyme Ethyl. **A5167:10-21**.

When aligned with the amino acid sequence of the parent G997 alpha-amylase, the amino acid sequence of the Spezyme Ethyl alpha-amylase has 100% identity ("at least 95% homology") to the G997 sequence, calculated using the GAP GCG "exact match" approach in the patent. **TE-126; A5113:22-5114:20; A5116:18-5117:1; A5158:16-5159:1**. When aligned with SEQ. ID NO. 3, the Spezyme Ethyl sequence has 98.967% identity ("at least 95% homology") to SEQ. ID NO. 3. **TE-127; A5118:22-5121:11; A5160:7-5161:15**. Thus, Spezyme Ethyl satisfies the percent homology requirements of claim 1 and claim 3.

Using SEQ. ID NO. 3 as a reference for numbering, the Spezyme Ethyl alpha-amylase has a deletion of the Arginine (R) and Glycine (G) amino acids at residues 179 and 180 when aligned and compared to its parent G997 alpha-amylase. **TE-126; A5159:2-14; A5260:21-5261:5; A5513:15-5514:12**. The deletion requirement of claim 1 is met. When aligned to SEQ. ID. NO. 3 alone, the Spezyme Ethyl alpha-amylase has a deletion of the Arginine (R) and Glycine (G) amino acids at the residues numbered 179 and 180. **A5119:22-5120:7; A5159:2-14; TE-127.** Thus, the deletion requirement of claim 3 is also met by Spezyme Ethyl. **TE-127; A5119:22-5120:7; A5159:2-14; A5260:21-5261:5, A5513:15-5514:12**. When aligned to G997, the Spezyme Ethyl sequence is identical, except that the 179,180 Arg (R) and Gly (G) residues are present in G997 and are deleted in Spezyme Ethyl (still using SEQ. ID NO. 3 for numbering). **TE-126; A5162:9-22; A5262:16-5263:16**. Thus, the requirements of claim 5 are met.

In sum, Spezyme Ethyl alpha-amylase satisfies each and every claim limitation of claims 1, 3, and 5 of the '031 Patent.

Genencor turned to Spezyme Ethyl, despite this infringement, in order to compete in the fuel ethanol market. Genencor's customers were demanding a more economical and thermostable alpha-amylase for years, demands Genencor could not satisfy. **A5032:3-5037:14**. G997 and Spezyme Fred did not do the job. **A5032:12-5039:11; A5046:14-21; A5048:13-5049:24.** Efforts to improve Spezyme Fred were unsuccessful. ***Id.*** Since its April 2004 launch, Spezyme Ethyl has enjoyed great success. **A1006**.

Genencor was so taken with Spezyme Ethyl that in 2004 it filed its own provisional patent application "relating to the Spezyme Ethyl technology." **TE-194, A8525.** The corresponding regular application has been published (**TE-202**) and boasts "novel variant alpha-amylase enzymes" wherein "the residues corresponding to R179 and G180 in *Bacillus stearothermophilus* are deleted." **TE-202, A8532.1 (Abstract), A8532.44 (claim 1)**; *see also* **A6538:22-6540:7; A6542:16-6543:5**. This was despite Suzuki (**TE-202, A8532.14-15 at ¶0013**) and Machius '95 (***Id.* at A8532.20, ¶[0095]**). Genencor stated, "a need exists for an alpha-amylase which is more

effective in commercial liquefaction processes" (***Id.* at 8532.15, ¶[0015]**). A particular goal was, "to provide an alpha-amylase having improved stability at high temperatures" (***Id.* at ¶[0017]**), as well as "improved stability in the absence of calcium ion" (***Id.* at A8532.24, ¶[0123]**). Accordingly, Genencor provided "a variant of a precursor *Bacillus stearothermophilus* alpha-amylase comprising deletions at one or more of the following positions R179 and G180 of the amino acid sequence shown in SEQ. ID NO. 3 and/or in a corresponding position in an alpha amylase which displays at least 90% identity with the amino acid sequence of SEQ. ID NO. 3." ***Id.* at A8532.15, ¶[0018]**. These alpha-amylases, "exhibit altered performance characteristics providing desirable and unexpected results" ***Id.* at A8532.22, ¶[0112]**. Those "which exhibit improved thermostability will be especially useful in starch processing and particularly in starch liquefaction." ***Id.* at A8532.22, ¶[0113]**.[3]

II. ARGUMENT

A. Claim Construction

Claim construction is a threshold inquiry in any assessment of patent infringement. *Athletic Alternatives v. Prince Mfg.*, 73 F.3d 1573, 1578 (Fed. Cir. 1996). First, the meaning of the patent claim is ascertained, and second, the accused product or method is compared with the claim as properly interpreted; *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370 (1996). Claim construction is a question of law. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

The fundamental starting point is with the claims themselves. *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115-16 (Fed. Cir. 2004) (a "bedrock principle" is that "the claims of a patent define the invention"); *Markman*, 52 F.3d at 979-80; *Vitronics*, 90 F.3d at 1582. A proper construction must give meaning to every claim limitation, *see Harris Corp.*

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[3] Genencor's 2004 application was long after Novozymes filed its earliest U.S. application in 1996 (**TE-100, A7002**), and after Genencor knew about Novozymes' application. **A5014:4-14; A5663:16-A5664:21.**

v. IXYS Corp., 114 F.3d 1149, 1152 (Fed. Cir. 1997), and a given term has the same meaning throughout the claims. *Southwall Techs. v. Cardinal IG Co.*, 54 F.3d 1570, 1579 (Fed. Cir. 1995). Other considerations include the context of words surrounding a claim term, *ACTV v. Walt Disney Co.*, 346 F.3d 1082, 1088 (Fed. Cir. 2003), as well as similarities and differences among the claims. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314-15 (Fed. Cir. 2005) (*en banc*). Common words in a claim should have their ordinary meaning "[w]ithout an express intent to import a novel meaning to them." *York Prods., Inc. v. Central Tractor & Farm Family Ctr.*, 99 F.3d 1568, 1572 (Fed. Cir. 1996). Thus, claim terms are given their customary meaning to one skilled in the art at the time of the invention, unless the specification defines them differently. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005); *Innova*, 381 F.3d at 1116.

The patent document is paramount. *Phillips*, 415 F.3d at 1315-17. It is meant to be a "concise statement for persons in the field." *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1119 (Fed. Cir. 2002). It will guide the person of ordinary skill to a proper understanding of the claims. "Importantly, the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim … but in the context of the entire specification." *Phillips*, 415 F.3d at 1313. "The specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication." *Vitronics*, 90 F.3d at 1582. "Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Id.* "The best source for understanding a technical term is the specification from which it arose, informed, as needed, by the prosecution history." *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1478 (Fed. Cir. 1998). This is the intrinsic record from which a correct claim construction proceeds. *Vitronics*, 90 F. 3d at 1582.

Although it is the best guide, the specification cannot be used to alter the claims, as by "reading a limitation from the written description into the claims." *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1340 (Fed. Cir. 2001). Likewise, a claim cannot be limited to the patent examples. *Phillips*, 415 F.3d at 1323; *SuperGuide Corp. v. DirecTV Enters., Inc.*, 358 F.3d 870, 875 (Fed. Cir. 2004).

Extrinsic evidence "can shed useful light on the relevant art" but is far "less significant than the intrinsic record." *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 862 (Fed. Cir. 2004) (*citation omitted*). Expert and inventor testimony, dictionaries and treatises may provide background guidance. *Phillips*, 415 F.3d at 1318-19. However, "[u]ndue reliance on extrinsic evidence poses the risk that it will be used to change the meaning of claims in derogation of the 'indisputable public records consisting of the claims, the specification and the prosecution history.'" *Id.* at 1319 (*citation omitted*).

In sum, '[t]he construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998).

1. Claim 1 of the '031 Patent

Claim 1 of the '031 patent reads as follows (**TE-100, A7040**):

> A variant of a parent *Bacillus stearothermophilus* alpha-amylase, wherein the variant has an amino acid sequence which has at least 95% homology to the parent *Bacillus stearothermophilus* alpha-amylase and comprises a deletion of amino acids 179 and 180, using SEQ. ID NO. 3 for numbering, and wherein the variant has alpha-amylase activity.

The intrinsic evidence provides clear meanings for the terms in claim 1.

The preamble, *i.e.*, introductory portion, of claim 1 recites "[a] variant of a parent *Bacillus stearothermophilus* alpha-amylase." A preamble that states only a purpose or intended use is not a claim limitation. However, the preamble here is necessary to give "life and meaning" to the claim and, therefore, it is a claim limitation. *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1257 (Fed. Cir. 1989). It is also a limitation, as here, when the body of the claim relies on antecedent language in the preamble. *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002). The preamble of claim 1 specifies the particular type of enzyme variant that is claimed.

Several claim terms warrant discussion.

(a) Variant

Claim 1 provides a "variant" of a parent *B. stearothermophilus* alpha-amylase. **TE-100, A7040**. The '031 specification states that a "variant" ("or mutant," ***Id.* at A7010, 5:49-50**) is the result of the deletion, substitution, or insertion of amino acids relative to a parent alpha-amylase. **A5138:23-5139:20**. Specifically (**TE-100 at A7009, 3:59-67**):

> The variants of the invention are variants in which: (a) at least one amino acid residue of the parent alpha-amylase has been deleted; and/or (b) at least one amino acid residue of the parent alpha-amylase has been replaced (i.e. substituted) by a different amino acid residue; and/or (c) at least one amino acid residue has been inserted relative to the parent alpha-amylase.

A "variant" is consistently a protein that is modified relative to a parent. This provides modified properties "relative to the parent enzyme." **TE-100 at A7008, 1:20-25, 2:61-63**. A parent is improved, "by judicial modification of one or more amino acid residues in various regions of the amino acid sequence of the parent alpha-amylase." ***Id.* at 7009, 3:17-22**; *see also* ***id.* at 5:49-57** (variant "deriving from an unmodified parent alpha-amylase"). This usage is also the ordinary meaning of "variant" in protein engineering. **A5138:23-5139:9** (Dr. Arnold); **A5203:2-11** (Dr. Alber); *see also* **TE-202, A8532.17 at ¶[0045]**.

In sum: a "variant" is an engineered protein that is the result of the deletion, substitution, or insertion of amino acids relative to an unaltered protein.

(b) Parent

Claim 1 provides a variant of a "parent" *B. stearothermophilus* alpha-amylase. **A7040**. The specification states that a parent is an antecedent protein that is altered to provide a variant protein:

> (a) "The present invention relates to alpha-amylase variants having improved properties relative to the parent enzyme (e.g. improved thermal and/or oxidation stability and/or reduced calcium ion dependency)" (**TE-100, A7008 at 1:21-24**);
>
> (b) "An object of the present invention is to provide alpha-amylase variants which -- relative to their parent alpha-amylase -- possess improved properties of importance, … e.g. increased thermal stability" (**TE-100, A7008 at 2:61-65**);

> (c) "A goal of the work underlying the present invention was to improve, if possible, the stability of, inter alia, particular alpha-amylases which are obtainable from Bacillus strains" (**TE-100, A7009 at 3:11-13**); and
>
> (d) "[I]t is in fact possible to improve properties of … such a parent alpha-amylase by judicial modification of one or more amino acid residues in various regions of the amino acid sequence of the parent alpha-amylase. The present invention is based on this finding" (**TE-100, A7009 at 3:18-23**).

The parent proteins, modified to make variants, are "alpha-amylases which are obtainable from *Bacillus* strains and which themselves have been selected on the basis of their starch removal performance." **TE-100, A7009 at 3:10-14**. The patent also identifies preferred mutations of representative parents to make variants of the invention. Such changes can be made to any suitable parent in corresponding fashion, *i.e.*, "in equivalent positions in the sequence of another alpha-amylase meeting one of the other criteria for a parent alpha-amylase." **TE-100, A7012 at 9:5-8;** *see also* ***id.*** **at 9:19-27, 10:1-3, 14-17, 36-37** (deleting equivalent residues for thermostability, "in another alpha-amylase meeting the requirements of a parent alpha-amylase in the context of the invention"), **10:52-54, 11:8-11, 11:35-36, 11:63-65** (same regarding calcium dependency).

These disclosures make plain that certain sequences given in the specification (*e.g.*, SEQ. ID NOs. 1, 2, 3 and 7) are "reference" sequences. Although proteins with these sequences may be used as suitable parents, they are not the only parents, and are not synonymous with the term "parent." A parent is often obtained from a naturally occurring (a/k/a wild-type) gene; it is unaltered relative to the variant. **A5150:13-5151:7**. The amino acid sequence of this unaltered protein is modified to produce a variant. *See* **TE-100, A7009 at 3:10-14** (parents are "alpha-amylases which are obtainable from *Bacillus* strains"); **TE-100, A7016 at 17:18-19** ("Naturally occurring enzymes may be genetically modified … as described").

The specification uses the ordinary meaning of "parent" in protein engineering. **TE-202, A8532.17 at ¶[0042]; A5150:13-5151:7**. According to Genencor's Dr. Alber (**A5203:5-11**):

> The parent is the source or ancestor of a protein and the variant is something derived from that parent. And the variant contains changes, which in the field are defined as substitutions, insertions and deletions.

In sum: a "parent" is an unaltered protein that is modified by the deletion, substitution, or insertion of amino acids to make a variant protein.

(c) *Bacillus Stearothermophilus* Alpha-Amylase

Claim 1 also provides that the parent is a "*Bacillus stearothermophilus* alpha-amylase." **TE-100, A7040.** *B. stearothermophilus* is a species of *Bacillus* bacteria, found in soil, that has a gene for producing alpha-amylase. **A5139:23-5141:5**. An alpha-amylase is an enzyme that catalyzes reactions to break down and liquefy starch. **TE-100, A7008 at 1:37-38; A1003, ¶¶D-H.** Thus, a "*B. stearothermophilus* alpha-amylase" enzyme is a protein having alpha-amylase activity that is produced by a *B. stearothermophilus* alpha-amylase gene. **A5138:19-5140:14**. The amino acid sequence of the enzyme can be experimentally determined. **A5058:5-16; A5163:3-16**. A fundamental goal of the invention is to improve the properties of actual enzymes by making variants. **TE-100, A7008 at 1:21-22; A5022:16-5027:14**. The improvement is by comparison with real enzymes that break down starch, not with predicted amino-acid sequences or "pre-proteins" translated from DNA but not yet finished. The actual variant (even if truncated when completely processed) is compared with the actual parent (even if truncated when completely processed). **A5207:25-5208:21; A6065:13-19; A6068:2-16; TE-161, A8369; A5164:6-17.**

In sum: a "B. stearothermophilus alpha-amylase" is the functional enzyme that is actually produced by the alpha-amylase gene from a B. stearothermophilus organism.

(d) Percent Homology

Claim 1 provides that the variant of the invention, "has an amino acid sequence which has at least 95% homology to the parent *B. stearothermophilus* alpha-amylase."**T E-100, A7040.** The '031 patent expressly discusses the meaning of "percent homology" in the context of the invention, as follows (**TE-100, A7009 at 4:36-49**):

> An amino acid sequence is considered to be X % homologous to the parent alpha-amylase if a comparison of the respective amino acid sequences, performed via known algorithms, such as the one described by Lipman and Pearson in Science 227 (1985) p. 1435, reveals an identity of X %.

The patent equates "percent homology" with "percent identity," and refers particularly to the GAP GCG program. *Id.*; **A5525:5-9**. The specification gives a clear meaning for "percent homology," and also provides distinct guidance for how to implement that definition. *Vitronics,* 90 F.3d at 1582.

Two sequences are aligned according to known algorithms, which find an optimum number of matches between them. **A1005, ¶¶N, O; A5107:21-5018:2: A5108:21-A5109:10.** Then, the matches are counted. **A5110:22-5111:6**. As with any "percent," this calculation divides a numerator by denominator, multiplied by 100%. ***Id.*** In the GAP program, the number of exact matches between two amino acid sequences (the numerator) is divided by the number of these amino acid residues where there are residues present in both sequences (the denominator). **A5111:2-6**; *see also* **A5111:10-5112:12**. When both sequences have a residue present at a position in the numbered alignment, whether or not they are the same, that position is counted in the denominator. **A5111:18-5112:8.** When only one sequence has a residue present at a given position, with nothing at that position in the other sequence, the resulting gap is not counted. **A5110:22-5111:17.** The number of exact matches (positions where the aligned residues in both sequences are identical), is used for the numerator. **A5110:22-5112:8-** "Percent identity takes the sum of all the matching residues where there is a corresponding part in both sequences." **A5111:2-4**. This answers the question: "How much of one sequence is present in the other sequence?" **A5118:3-10**. This is a routine question in the field of protein engineering, answered in a standard way. **A5117:3-5118:14**. Percent homology is calculated according to a standard percent identity formula. **A5141:21-5142:3.** "The patent clearly states that the GAP program of GCG may suitably be used. That leads you to a particular calculation of that percent identity." **A5146:14-5147:1;** *see also* **TE-202, A8532.17 at ¶¶[0054-56].**

In sum: "Percent homology," as defined in the '031 patent, means a percent identity calculation according to the standard whereby the number of exactly matching amino acid residues in two sequences is compared to the total number of residue positions that are present in both sequences, expressed as a percent, e.g., as implemented by the GAP GCG program.

(e) Deletion of Amino Acids 179 and 180, Using SEQ. ID NO. 3 For Numbering

Each variant of claim 1, compared to its parent, "comprises a deletion of amino acids 179 and 180 using SEQ. ID NO. 3 for numbering." **TE-100, A7040**. SEQ. ID NO. 3 is a reference sequence, given in the patent, and used to specify the positions of matching amino acid residues in a sequence alignment. **TE-100, A7040 at 65:10-66:19; A5142:5-23; A5639:5-18.** "For numbering" means that SEQ. ID. NO. 3 is expressly for reference; it is not claimed as the parent. The positions of residues in an alignment (between parent and variant) are assigned according to corresponding positions (residue numbers) in SEQ. ID. NO. 3. In claim 1, the amino acids of a parent sequence that align with positions 179 and 180 of SEQ. ID. NO. 3 are present in the parent sequence, but are not present in the aligned variant sequence. **A5143:3-10**. This is the plain meaning of "for numbering," and is consistent with the customary use of reference sequences in the art. **A5142:5-14; A5639:11-18**; **TE-202, A8532.17 at ¶[0057]**.

In sum: "a deletion of amino acids 179 and 180 using SEQ. ID NO. 3 for numbering." means that the amino acids present at positions 179,180 of the parent are deleted from the variant, when the amino acid positions of the aligned parent and variant are numbered according to amino acid position numbers of SEQ. ID. NO. 3.

(f) Alpha-Amylase Activity

"Alpha-amylase activity" means: an enzyme that is able to break apart starch complexes and convert starch into smaller, simpler groups of glucose molecules, by degrading or breaking specific chemical bonds, called the "alpha-1,4-glucosidic bonds," between the groups of glucose molecules that make up a complex starch molecule. **A1003**.

2. Claim 3 of the '031 Patent

Claim 3 of the '031 patent reads as follows (**TE-100, A7040**):

> A variant alpha-amylase, wherein the variant has at least 95% homology to SEQ. ID NO. 3 and comprises a deletion of amino acids 179 and 180, using SEQ. ID NO. 3 for numbering and wherein the variant has alpha-amylase activity.

Claim 3 is unambiguous, and several of its terms are also in claim 1. These terms have the same meaning. *Southwall,* 54 F.3d at 1579 (terms "cannot be interpreted differently in different claims").

The preamble of claim 3 recites "[a] variant alpha-amylase." As above, this preamble limits the claim, and the terms have the same meaning as in claim 1.

"[A]t least 95% homology" is construed as in claim 1. Thus, the language "wherein the variant has at least 95% homology to SEQ. ID NO. 3" means that the amino acid sequence of the variant must have at least 95% identity to the amino acid sequence of SEQ. ID NO. 3, using an "exact match" algorithm for percent identity equivalent to that of GAP GCG.

The language "comprises a deletion of amino acids 179 and 180, using SEQ. ID NO. 3 for numbering" is also construed the same way in claim 3 as in claim 1. Likewise for the language, "the variant has alpha-amylase activity."

Claim 3 is for a variant alpha-amylase with alpha-amylase activity. When aligned with SEQ. ID NO. 3, the variant is at least 95% identical to SEQ. ID NO. 3 (not a parent *per se*), using the "exact match" algorithm for percent identity. The variant differs from SEQ. ID NO. 3 (not a parent *per se*) by a deletion of residues at positions 179 and 180 of SEQ. ID NO. 3, used for numbering.

3. Claim 5 of the '031 Patent

Claim 5 of the '031 patent reads as follows (**TE-100, A7040**):

> A variant of a *Bacillus stearothermophilus* alpha-amylase, wherein the alpha-amylase variant consists of a deletion of amino acids 179 and 180, using SEQ. ID NO. 3 for numbering.

Claim 5 is unambiguous and clear. Several of its terms are found in claims 1 and 3, and these terms have the same meaning. *Southwall,* 54 F.3d at 1579.

The preamble of claim 5 recites "[a] variant of a *Bacillus stearothermophilus* alpha-amylase." The preamble is limiting, like claims 1 and 3, and each term has the same meaning as in claims 1 and 3. Claim 5 provides a variant protein expressed by an alpha-amylase gene, which has been (i) obtained from *Bacillus stearothermophilus*, and (ii) deliberately manipulated by protein

engineering, *i.e.*, by altering the *B. stearothermophilus* gene to produce an addition, deletion, or substitution of the amino-acid sequence of the *B. stearothermophilus* protein.

The limitation requiring "a deletion of amino acids 179 and 180, using SEQ. ID NO. 3 for numbering" also should be construed as it is for claims 1 and 3. However, unlike claims 1 and 3, claim 5 states that the variant, "consists of" this deletion (**A7040**). The transition term "consists of" signals that the list of ensuing elements is closed. The claim excludes additional, unrecited components, *i.e.*, other amino acid deletions, substitutions, or additions. *AFG Indus., Inc. v. Cardinal IG Co.*, 239 F.3d 1239, 1245 (Fed. Cir. 2001). Claim 5 specifies that the amino acid sequence of the variant differs from the *B. stearothermophilus* alpha amylase only by deletion of the residues at positions 179 and 180, using SEQ. ID NO. 3 as a reference for numbering.

B. Genencor's Spezyme Ethyl Product Infringes '031 Claims 1, 3 and 5

The alpha-amylase in Genencor's Spezyme Ethyl product satisfies each and every limitation of claims 1, 3, and 5 of the '031 Patent. 35 U.S.C. §271. Therefore, literal infringement is present. *Norian Corp. v. Stryker Corp.*, 363 F.3d 1321, 1331-32 Fed. Cir. 2004).

1. Spezyme Ethyl Infringes Claim 1 of the '031 Patent

Spezyme Ethyl is unequivocally "a variant of a parent *B. stearothermophilus*" according to claim 1. **TE-100, A7040**. Spezyme Ethyl is derived from G997, a *B. stearothermophilus* alpha-amylase. G997 is the parent of Spezyme Ethyl. **TE-194, A8525; TE-161, A8365-66; A5148:20-5149:3, A5150:7-5151:7; A5161:25-5162:8; A5259:8-5261:1**. *Spezyme Ethyl is an engineered protein that is the result of the deletion, substitution, or insertion of amino acids relative to an unaltered protein:* G997. ***Id.*** The G997 "parent" is *an unaltered protein that is modified by the deletion, substitution, or insertion of amino acids to make a variant protein:* Spezyme Ethyl. ***Id.*** G997 is also a "*B. stearothermophilus* alpha-amylase": *it is the enzyme that is actually produced by the alpha-amylase gene from a wild-type B. stearothermophilus organism*: the gene from "*Bacillus stearothermophilus* strain ASP154, ATCC deposit no. 39,709" a/k/a G997. **TE-194, A8521, A8525; TE-161, A8365-66; A5259:8-5261:1**.

The claim 1 variant has alpha-amylase activity. **TE-100, A7040; A1003**. Genencor admits Spezyme Ethyl has alpha-amylase activity. **TE-194, A8525; TE-134, A8355; A5159:17-23**.

Claim 1 specifies that the variant differs from the parent by a deletion of the residues at positions 179 and 180 of the parent, "using SEQ. ID NO. 3 for numbering." **TE-100, A7040**. Plus, "the variant has an amino acid sequence which has at least 95% homology to the parent." **TE-100, A7040**. When Spezyme Ethyl and G997 are aligned, and percent homology is calculated according to properly construed claims, Spezyme Ethyl has the claimed 179,180 deletion and has at least 95% homology to G997. **TE-126; A5113:22-5114:20; A5116:18-5117:1; A5158:16-5159:14; A5260:21-5261:5; A5513:15-5514:12**.

Dr. Jorgensen sequenced Spezyme Ethyl and obtained the same amino sequence as is admitted by Genencor (**TE-125, A8345; A5071:25-5072:10; TE-194, A8521-22**), and to which the parties have stipulated (**A1006-7**). Thus, the amino acid sequence in **TE-125** is the sequence of Spezyme Ethyl. The amino acid sequence of G997 is set forth in **TE-199** and **TE-226**.

Dr. Devereaux (**A5101:14-5103:16; TE-131**), performed a sequence alignment between Spezyme Ethyl (**TE-125**) and G997 (**TE-199**). He used version 10 of the GAP GCG program, with default parameters from version 7, as in the patent. **TE-100, A7009 at 4:36-45**. The result, using the GAP formula for percent identity, would be the same with version 7.3. **A5116:18-5117:1**. The alignment confirms that the sequences are identical, except that residues R,G at positions 179 and 180 of G997, are deleted in Spezyme Ethyl. **TE-126; A5162:9-22; A5262:16-263:16**.

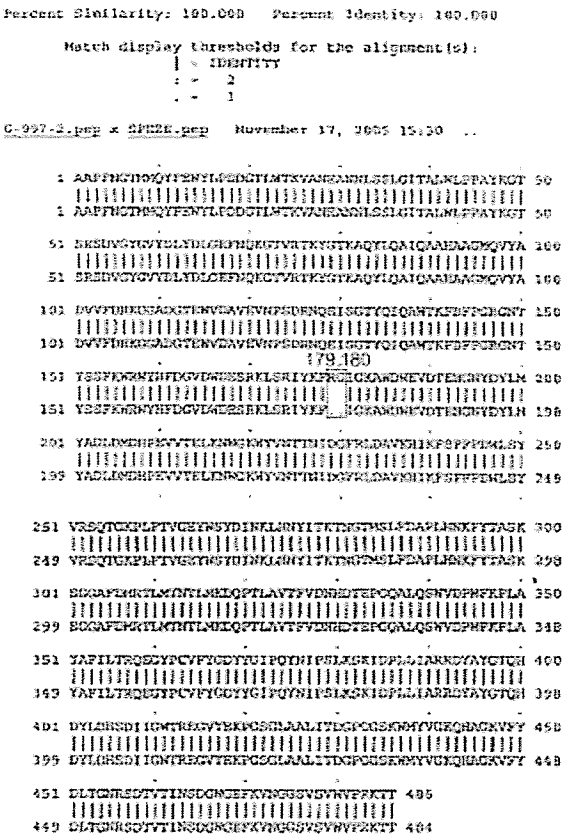
The GAP program calculated the percent identity between the two sequences as 100%. **TE-126, A8347**; **A5113:22-5115:20**; **A5158:18-5159:1**. The alignment shows that all 484 amino acids of Spezyme Ethyl are present in the 486 amino acid sequence of G997. **TE-126, A8347-8; A5113:22-5114:20; A5116:18-5118:15; A5158:16-5159:1** Thus, all (100%) of the Spezyme Ethyl sequence is present in G997. Spezyme Ethyl has "at least 95% homology" to the G997 parent. ***Id.***

Dr. Devereaux also used GAP to align Spezyme Ethyl with SEQ. ID. NO. 3 **TE-127, A8349-50**; **A5118:22-5121:11**. This alignment confirms that that Spezyme Ethyl does not have the

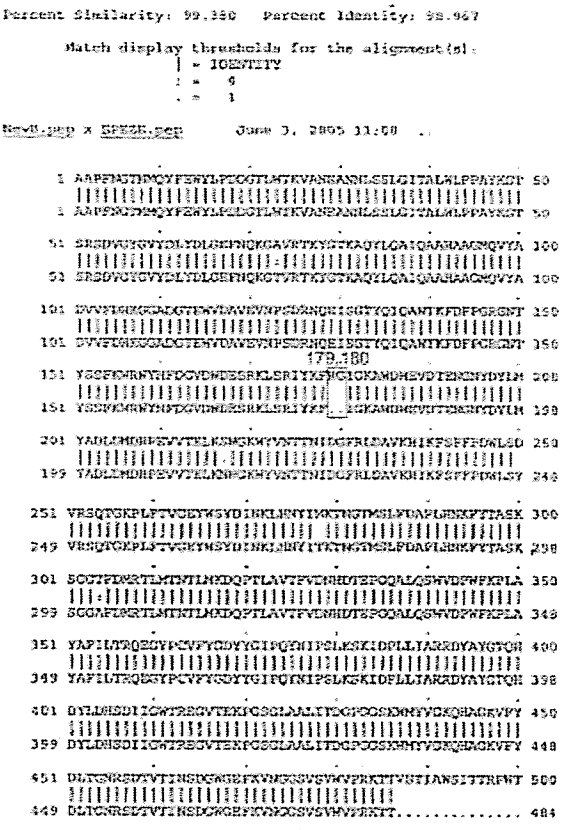
two amino acids, R and G, at positions 179 and 180 of SEQ. ID. NO. 3. ***Id***. When SEQ. ID No, 3 is used for numbering, residues 179,180 are deleted. Likewise, **TE-126** and **TE-127** prove that G997 and SEQ. ID. NO. 3 have the same numbering. **A5119:22-5120:7**; **A5159:2-14; A5162:9-22**. The percent identity was 98.967%. **TE-127, A8349**; **A5118:22-5121:1**; **A5160:7-5161:12**.

Annotated excerpts from the alignment reports, showing infringement, are shown below.

TE-126
SPEZYME ETHYL (Bottom Row) ALIGNED WITH G997 (Top Row)



TE-127
SPEZYME ETHYL (Bottom Row) ALIGNED WITH SEQ. ID NO. 3 (Top Row)



Per claim 1, Spezyme Ethyl "comprises a deletion of amino acids 179 and 180, using SEQ. ID. NO. 3 for numbering:" *the amino acids present at positions 179,180 of the parent are deleted from the variant, when the amino acid positions of the aligned parent and variant are numbered according to amino acid position numbers of SEQ. ID. NO. 3*.

All of the limitations of claim 1 are found in Spezyme Ethyl. It is a variant of a parent *B. stearothermophilus* alpha-amylase having the amino acid sequence of G997. Spezyme Ethyl's sequence aligns exactly to the G997 sequence, except for the two amino acids at positions 179 and 180. These positions are the same as positions 179 and 180 of SEQ. ID. NO. 3 in the patent. These two amino acids are present in G997 and are deleted in Spezyme Ethyl. When percent identity is calculated, using the "exact match" algorithm of GAP GCG, Spezyme Ethyl has 100% homology to G997, which is "at least 95%."

2. Spezyme Ethyl Infringes Claim 3 of the '031 Patent

Claim 3 specifies a variant alpha-amylase. **TE-100, A7040**. Spezyme Ethyl is derived from and is a variant of G997, a *B. stearothermophilus* alpha-amylase. **TE-194, A8525; TE-161, A8365-66; A5148:8-149:18; A5150:7-151:7; A5161:25-5162:8; A5259:8-5261:1; A5513:15-5514:12**. As in claim 1, Spezyme Ethyl is a "variant": *it is an engineered protein that is the result of the deletion, substitution, or insertion of amino acids relative to an unaltered protein:* G997. ***Id.*** G997 is an "alpha-amylase" (**id.**), and both G997 and Spezyme Ethyl have alpha-amylase activity. **TE-194, A8521, 25; TE-134, A8355; A5159:17-23.** There can be no doubt that Spezyme Ethyl is "a variant alpha-amylase" of claim 3, and it has alpha-amylase activity. ***Id.***

Claim 3 specifies that the variant differs from SEQ. ID. NO. 3 by a deletion of the two amino acids at positions 179 and 180, "using SEQ. ID NO. 3 for numbering." **TE-100, A7040**. Spezyme Ethyl has this deletion compared to SEQ. ID. NO. 3. **TE-127, A8349-50**; **A5118:22-A5121:11; A5160:16-5161:5**. The amino acids aligned at positions 179 and 180 of SEQ. ID. NO, 3 are deleted in Spezyme Ethyl. ***Id.***

A percent identity of 98.967% was calculated for the alignment of Spezyme Ethyl and SEQ. ID. NO. 3. ***Id.*** This is "at least 95%." ***Id.*** When Spezyme Ethyl and SEQ. ID. NO. 3 are aligned, and percent homology is calculated using the standard percent identity method exemplified by GAP, Spezyme Ethyl is at least 95% homologous to SEQ. ID. NO. 3. ***Id.***

Claim 3 is infringed. Spezyme Ethyl is a "variant alpha-amylase," and more specifically is derived from an identified *B. stearothermophilus* alpha-amylase strain. **TE-194, A8521, 8525**. When the Spezyme Ethyl sequence is aligned to SEQ. ID. NO. 3, the two amino acids at positions 179 and 180 are deleted. **TE-127**. When percent identity is calculated, Spezyme Ethyl shows a 98.967% homology to SEQ. ID NO. 3, which is "at least 95%." ***Id.***

3. Spezyme Ethyl Infringes Claim 5 of the '031 Patent

Claim 5 provides a "variant of a *Bacillus stearothermophilus* alpha-amylase." **TE-100, A7040**. As with claims 1 and 3, Spezyme Ethyl is derived from and is a variant of G997, which in turn is an alpha-amylase that originates from a specific *B. stearothermophilus* alpha-amylase. **TE-194, A8521, 8525**. Claim 5 also states that the variant "consists of a deletion of amino acids 179 and 180, using SEQ. ID. NO: 3 for numbering." **TE-100, A7040**. The Spezyme Ethyl sequence differs from G997 by only these two amino acids. The residues R,G at positions 179,180 of G997 are deleted in Spezyme Ethyl, using the residue numbering of SEQ. ID NO. 3. **TE-126; A5162:9-22; A5259:23-5261:5**. The limitations of claim 5 are met by Spezyme Ethyl.

In sum, Spezyme Ethyl literally infringes claim 1, 3, and 5.

C. The '031 Patent Is Valid

An issued patent is presumed valid, and can be nullified only by clear and convincing evidence. 35 U.S.C. § 282; *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999); *Robotic Vision Sys., Inc. v. View Eng'g, Inc.*, 189 F.3d 1370, 1377 (Fed. Cir. 1999). This burden may be especially difficult when a defendant relies on the same prior art that was considered during prosecution of the patent. *Metabolite Labs., Inc. v. Laboratory Corp. of Am. Holdings*, 370 F.3d 1354, 1368 (Fed. Cir. 2004) (*citing Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1467 (Fed. Cir. 1990)), *cert granted*, 126 S. Ct. 601 (2005). To make a real difference, additional prior art must not be cumulative; it must add to what the PTO has already considered. *Id.*

D. The '031 Patent Claims Are Not Obvious

A claimed invention can be obvious and unpatentable if "the differences between the claimed invention and the prior art are such that the claimed invention, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which it pertains." 35 U.S.C. § 103(a); *Graham v. John Deere Co.*, 383 U.S. 1, 13-14 (1966). "The obviousness standard, while easy to expound, is sometimes difficult to apply. It requires the decision maker to return to the time the invention was made." *Uniroyal, Inc. v. Rudkin-Wildy Corp.*, 837 F.2d 1044, 1050 (Fed. Cir. 1988). This is a legal question based on underlying findings of fact. *In re Dembiczak*, 175 F.3d 994, 998 (Fed. Cir. 1999). The answer will depend on (1) the scope and content of the prior art, (2) differences with claims at issue, (3) the level of ordinary skill in the art, and (4) objective evidence or secondary considerations. *Graham*, 383 U.S. at 17-18.

Most inventions arise from a combination of old elements. *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). However, identifying each element in the prior art is not sufficient preclude a patent for the combination. *Id.* The prior art must have suggested the combination to make or carry out the invention, and must "have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). The suggestion and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure, and not from hindsight. *Id.*; *see In re Rouffet*, 149 F.3d at 1357-58. "Obvious to try" has long been held not to constitute obviousness. *In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995). A general incentive, for example to try Suzuki's deletions elsewhere, does not make obvious a particular result. *Id.* An invitation to experiment cannot make an invention obvious. *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). In particular, success is not reasonably expected when its kind or degree was unpredictable. *In re Soni*, 54 F.3d 746, 750-51 (Fed. Cir. 1995) (substantially improved and unexpected). An invention is not obvious when its results were unexpected. *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006). Likewise, an invention that satisfies a long-felt need, overcomes past failures, or is a distinct

commercial success, is not likely to be obvious. *Fromson v. Advanced Offset Plate*, 755 F.2d 1549, 1556-58 (Fed. Cir. 1985) ("evidence of secondary considerations . . . 'may often be the most probative and cogent evidence in the record'") (citation omitted).

1. Claims 1, 3 and 5 Provide Unexpected Results

During the '031 prosecution, the PTO Examiner considered the *B. stearothermophilus* 179,180 deletion obvious under 35 U.S.C. §103(a). She rejected claims to these variants based on a combination of Suzuki (**TE-115**) and Bisgärd-Frantzen (**TE-177**). **A5011:1-16; TE-101 at A7627-28**. Suzuki describes mutants of an alpha-amylase enzyme from another *Bacillus* species – *B. amyloliquefaciens* ("BAN" or "BAA"). Some of these mutants were modified to be more like a different alpha-amylase, from *B. licheniformis* ("BLA"), and they had improved thermostability compared to the wild-type BAN alpha-amylase they came from. One BAN mutant had a deletion of two amino acids: Arginine 176 (R176) and Glycine 177 (G177). Bisgärd-Frantzen notes alpha-amylases from *B. amyloliquefaciens*, *stearothermophilus* ("BSG"), and *licheniformis*, provides a sequence alignment, and states that these alpha-amylases are highly homologous. **TE-177, A8413:23-24**; **TE-101, A7628:7-9.** Based on this, the Examiner concluded that it would have been obvious to make Suzuki's BAN 176,177 deletions in the corresponding 179,180 positions of BSG, with an expectation of similar improvement. **TE-101 at A7628:13-19.**

Novozymes overcame this rejection by submitting a Declaration from co-inventor Dr. Torben Borchert, which described an experiment comparing the deletion of R179-G180 in BSG to Suzuki's deletion of R176-G177 in BAN. **TE-508**; **TE-101, A7739-56**. The experiment showed that the 179,180 BSG variant does not just provide a similar improvement: it is very much better. **A5641:10-19; A6518:8-6519:7; A6519:15-6520:13; A6522:7-12; A6529:7-19; A6550:16-22**. These results, confirmed at trial, demonstrate that the claimed invention is not obvious; the claimed variants exhibit unexpected superior properties and advantages. *In re Soni*, 54 F.3d at 751. The improvement here was unforeseeable (**A5641:10-19; A6518:8-6519:7; A6519:15-6520:13; A6522:7-12; A6529:7-19; A6550:16-22**), which has been borne out by Genencor's initial failures

(**A5032:12-5039:11, A5046:14-21, A5048:13-5049:24.**), its adoption of the invention by Genencor, its commercial success (**A1006, ¶¶ V-Y**), and by Genencor's own patent application belatedly laying claim to the same subject matter (**TE-202**). *Mosinee Paper Corp. v. James River Corp.*, 22 U.S.P.Q. 2d 1657, 1661 (E.D. Wis. 1992).

Dr. Borchert made a fair comparison of a claimed 179,180 BSG variant with Suzuki's 176,177 BAN variant, and with the corresponding wild-type BSG and BAN alpha-amylases. **TE-508, A1008; A6092:11-14.** He selected conditions that are relevant to the industrial applications where these enzymes are used, including low calcium, and an industrial temperature of 80°C that was suitable for comparing all four enzymes. **A6092:15-25; A6534:2-14; A6536:2-25**. All of the enzymes were tested under the same conditions, as stated in the Declaration. **A6094:8-17; TE-508, A8858 ¶5.** Dr. Borchert used equipment that made it reasonable to forego a pre-heated buffer (**A6538:19-20**), and which would not have changed the qualitative results and overall conclusion. **A6545:25**. Thermostability was compared by measuring the residual activity of each enzyme over time, with two readings per sample. **A5808:10-16.** Unreliable measurements were not counted, as any good scientist would do. **A6549:19-20**. The half-life of each enzyme was calculated using standard techniques, including a log plot of the data and regression analysis. **A5803:17-5804:5; A6532:1-10**. The half-life is the time at which half (50%) of the initial alpha-amylase activity (100%) is still present under given conditions. **A5787:20-5788:4**. For each enzyme, the relative improvement of wild-type to variant was calculated. **A5794:3-17; A6532:11-6533:22**.

The experiment showed that Suzuki's BAN deletion increased thermostability 11-fold compared to the BAN wild-type enzyme. **A6532:11-14.** The corresponding BSG deletion caused a 63-fold increase in thermostability. ***Id.* at 15-23; TE-508, A8861**. The relative effect in BSG is 5.7-fold greater than in BAN (reported as 5-6 fold in the Declaration). **TE-508, A8660**; **A6533:18-6534:1.** Indeed, the BSG variant is still potent after exposure to high heat for 4,200 minutes (~ 3 days), and longer. **A6534:24-6535:4**. According to Dr. Arnold, "[T]he practical effect is very apparent." ***Id.*** "In fact, after three days it [the BSG variant] has more than half of its activity. So

this is an enzyme that keeps working after days at 80 degrees." ***Id.*** This has a definite commercial impact, especially in fuel ethanol production where alpha-amylases must work for hours at high temperatures and low calcium. **A6534:7-14; A6535:17-19.** Genencor itself admits that a lesser enzyme was unsuitable for demanding real-world conditions, and could not compete. **A5034:4-10; A5036:23-5037:14.**

No one could have predicted so great a leap forward. **A5722:1-4; A6550:16-22.** It was a difference in kind and not just in degree. Before the invention in 1995, no one could have expected that a BSG enzyme with a half-life of ~1.5 hours at 80°C (**TE-508, A8860 ¶7**) could be increased to more than three days. **A6534:24-6535:4.** The closest prior art BAN and BAN variant had half-lives of less than 1 minute and less than 10 minutes under the same conditions. **TE-508, A8860, ¶7.** Dr. Arnold found that an observed 63-fold improvement in BSG, or a 55 to 77-fold improvement ("the whole range of possibilities") (**A6549:1-6**), was unexpected and non-obvious, even with Genencor's critique. **A6550:16-19.** Dr. Borchert himself was surprised. **A5640:19-5641:19.** Dr. Alber had nothing helpful on this point. Dr. Klibanov said that anything less than an order of magnitude difference is unsurprising, but he did not support this assumption (**A5819:22-24**), and overlooked important industrial advantages. **A6534:19-6535:19; A5018:20-5019:1; A5051:3-7; A6550:16-22.** Dr. Zeikus testified that there was, at best, a 50/50 chance that the 179,180 BSG deletion would even work. **A6107:2-13.** Genencor's Dr. Machius testified that in 1995, even with Suzuki, Bisgärd-Frantzen, and Machius '95, a person of ordinary skill:

> [W]ould not have been able to predict the magnitude of stabilization in BSG, or to compare, or to know if there was any stabilization at all.

A5721:21-A5722:4.

Genencor's own patent application (**TE-202**) discloses and claims the same BSG variants. **TE-202, A8532.1 (Abstract), A8532.44 (claim 1); A6538:25-6540:6; A6542:20-6543:5.** While citing Suzuki and Machius '95 (**TE-202, A8532.14 at ¶¶[0013]-[0014], A8532.20 at ¶[0095]**), Genencor describes the 179,180 BSG variants as "providing desirable and unexpected results," and having "superior properties." ***Id.*** **at A8532.22, ¶[0012], A8532.24, ¶[0123].**

Significantly: Genencor has not provided any experiments or data to challenge these conclusions. Second-guessing the experiment, with litigation hindsight, cannot be compelling evidence that the claimed BSG variants are not as good as they really are, or that they are conclusively obvious and unpatentable. *Electro Med. Sys., S.A. v. Cooper Life Scis., Inc.* 34 F.3d 1048, 1055 (Fed. Cir. 1994) (no tests performed, "lack of hard evidence," and "opinion testimony unsupported by any backup" were unpersuasive). As Dr. Arnold recognized (**A6650: 3-15**):

> [W]e've looked at … every possible criticism. And my conclusion after seeing all of this is that it's a fair representation of what actually is going on with those enzymes. I would also like to mention that I have seen no counter data. This is not rocket science here … If this were wrong, if Borchert's data were far from the truth, I think I would have seen those data from some other place.

The claimed '031 variants provide an unpredictable and commercially important advance, and are patentable over the closest prior art.

2. Machius Does Not Make the Claimed Variants Any Less Unexpected

Machius '95 does not add anything of value to the cited prior art. **A6530:3-8**. The secondary structural elements proposed for BLA, from non-public X-ray coordinates (**A5718:1-15**), did not forecast the very highly improved thermostability of the claimed BSG variants. The Machius loop theory does not address, measure, or even hint at the magnitude of improved thermostability that might be realized for other variants. **A5721:21-5722:4**. Scientists toss up theories all the time (**A6526:5-6; A6527:19-23**), and Machius itself acknowledged that none of the theories was satisfactory. **TE-173, A8384**. In particular, the lack of further structural information about BAA and the Suzuki mutants was acknowledged as fatal (***Id.* at A8384-85**), to say nothing of the fact that there is no structural data about BSG at all.

According to Dr. Machius himself, the Machius '95 paper posits that the region corresponding to Suzuki's double-deletion in BAN is a "loop" on the surface of Domain B in BLA, which is enlarged in BAA by two extra residues. Theoretically, this could cause increased mobility and decreased thermal stability of BAN v. BLA. **A5703:15-18; A5709:24-5710:11**. Nevertheless,

Machius '95 does not provide any additional predictability, as Dr. Machius himself confirmed. **A5721:21-5722:4** (unable to predict fact or magnitude of stabilization in BSG).

Further, there were many problems with the BLA crystal structure referred to in Machius '95 (**TE-173**). It was not a reliable model from which to make predictions, and added nothing significant to what already could be taken from Suzuki, with or without Bisgärd-Frantzen. Whether Suzuki could be extrapolated to other mutants that would work, and whether they would work as well as Novozymes discovered, was unknown and unforeseeable, whether or not the artisan in 1995 was aware of the Machius "loop." **A6529:11-15**. As Dr. Arnold explained (**A6527:19-23**):

> So here we have this history. Klibanov has a hypothesis. Suzuki has a hypothesis. Janecek has a hypothesis. Machius has a hypothesis. In 1998, this is as far as I can go. There is yet another hypothesis and everybody else says everybody is wrong.

The Igarashi article showed further that "[t]he specific deletion that we're talking about made in that enzyme, while stabilizing, had a smaller effect than in the deletion had in the Suzuki enzyme, BAN." **A6529:10-15**. So, even after Suzuki and Machius, "you can't predict what the [*sic*] effect the deletion has." **A6529:17-18**. "There are no recipes for success for protein engineering in these recipes -- in these references." **A6529:24-6530:2**. "There is no additional information in the Machius reference." **A6530:7-8**.

Far from pointing the way to new and better variants, Machius '95 added more confusion to the literature. **A6530:3-8.** The loop idea is floated, and other theories trying to explain thermostability are discussed, but none are satisfactory, *e.g.*, because crucial data is missing. **TE-173, A8384.** Machius actually shows that engineering alpha-amylases to be more thermostable was (and is) an uncertain art. Genencor's Dr. Zeikus agreed (**A6103:17-22**) and added his own idea that "additional salt bridges is the feature that makes BLA more stable" (**A6524:21-A6525:9**) -- not the loop, or any of the other ideas. **A6504:5-20; TE-178, A8511.** No one in 1995, or today, knows why one alpha-amylase is more thermostable than another. No one could rely on Machius '95 to predict how successful the '031 variants would be. Dr. Machius himself admitted that "[l]oops, in general,

can have any effect" and "knowing something that is a loop can either stabilize [a protein] or might destabilize it if you change that loop." **A5720:20-5721:3,** *see also* **A5721:19-5722:4**. At best, Machius is cumulative and the '031 invention is patentable.

3. Other Secondary Considerations Belie a Finding of Obviousness

Objective guideposts, or "secondary considerations," help to avoid hindsight and promote a fair adjudication on questions of obviousness. *Graham*, 383 U.S. at 17-18; *In re Rouffet*, 149 F.3d at 1355, 1357-58 (secondary considerations are essential components of the obviousness determination). These considerations include (i) long felt need, (ii) failure of others, and (iii) commercial success. *Graham*, 383 U.S. at 17-18; *In re Rouffet*, 149 F.3d at 1355.

Here, there was a long felt need. Dr. Crabb testified that Genencor's customers were in need of a more economical and thermostable alpha-amylase for several years, a need Genencor could not satisfy until Spezyme Ethyl was on the market. **A5032:19-5033:9**. Genencor's G997 and Spezyme Fred products were not good enough (**A5034:4-5035:2; A5037:3-14**), nor was Genencor able to improve Spezyme Fred. **A5046:14-21; A5048:14-5049:24.**

Spezyme Ethyl was also a commercial success. It finally gave Genencor an economically efficient alpha-amylase with sufficient thermostability to compete in the fuel ethanol liquefaction market. In just two years, Genencor's total annual sales of Spezyme Ethyl have almost tripled. **A1005**. Since its introduction, Spezyme Ethyl has enjoyed great success, at the direct expense of Novozymes. **A6028:14-22.**

When the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988) (commercial success of infringing product demonstrated non-obviousness).[4] Genencor admits that it needed Spezyme Ethyl to

[4] Novozymes is selling a different alpha-amylase, covered by a different patent. Nevertheless, Spezyme Ethyl is a highly successful commercial embodiment of the '031 claims, which succeeded where other efforts failed. **A6028:14-22.**

compete successfully. **A5032:19-5033:9**. This commercial success, and that others tried and failed to reach a solution, favors a finding of non-obviousness. *Id.* at 1391.

In addition, Genencor filed its own patent application in 2004, claiming the Spezyme Ethyl alpha-amylase. **A6538:22-6540:7; A6542:16-6543:5**. All of the prior art asserted against the '031 patent is prior art to Genencor. Yet, Genencor represented to the PTO that Spezyme Ethyl is still non-obvious and patentable. As late as April 2005 (**TE-202, A8532.1**), Genencor said there was a long-felt need for alpha-amylases having improved thermostability (***Id.* at ¶[0015]**), and that 179,180 *B. stearothermophilus* variants provide unexpected, superior performance (***Id.* at ¶[0112]**), especially for starch liquefaction (**TE-202, [0111]**). This is telling evidence of non-obviousness. *Mosinee Paper Corp.*, 22 U.S.P.Q. 2d at 1661; *American Med. Sys., Inc. v. Medical Eng'g Corp.*, 794 F. Supp. 1370, 1386-87 (E.D. Wis. 1992) (attempt to patent same subject matter shows infringer "plainly believed" it was new and non-obvious); *Polaroid Corp. v. Eastman Kodak Co.*, 641 F. Supp. 828, 848 (D. Mass. 1985) (attempt to patent accused product is evidence that claims are valid against the prior art); *Colt Indus. Operating Corp. v. Index-Werke KG*, 205 USPQ 990, 1002 (D.D.C. 1979) (such actions "are of significant evidentiary value in showing the thinking of those skilled in the art and, as such, tend to show that the patented invention was not obvious").

E. There Was No Inequitable Conduct And The Patent Is Enforceable

Patent applicants and their attorneys have a duty of candor in the PTO. 37 CFR § 1.56 (1992). To establish a breach of that duty, or 'inequitable conduct," it must be conspicuously shown "that material information was intentionally withheld for the purpose of misleading or deceiving the patent examiner." *Allied Colloids, Inc. v. American Cyanamid Co.*, 64 F.3d 1570, 1578 (Fed. Cir. 1995). Materiality and intent are distinct factual inquiries, and must each be shown by clear and convincing evidence. *Purdue Pharma L.P. v. Endo Pharms, Inc..*, 438 F.3d 1123, 1128-29 (Fed. Cir. 2006); *Digital Control, Inc., v. Charles Mach. Works*, 437 F.3d 1309, 1313 (Fed. Cir. 2006). Whether information is material is determined by PTO regulations. *Purdue Pharma,* 438 F.3d at 1129. Information is material to patentability when (37 CFR § 1.56 (1992):

> it is not cumulative to information already of record or being made of record in the application, and (1) it establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or (2) it refutes, or is inconsistent with, a position the applicant takes in (i) opposing an argument of unpatentability relied on by the [PTO] or (ii) asserting an argument of patentability.

This was the standard after 1992 and during the '031 prosecution.[5] *Purdue Pharma,* 438 F.3d at 1129. Information is categorically not material if it is cumulative of what was already before the PTO, *i.e.*, "if the reference teaches no more than what a reasonable examiner would consider to be taught by the prior art already before the PTO." *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1574-75 (Fed. Cir. 1997); *see also Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1582 (Fed. Cir. 1991). Less relevant information is not material either. *Pro-Mold and Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1576-77 (Fed. Cir. 1996); *Halliburton Co. v. Schlumberger Tech. Corp.*, 925 F.2d 1435, 1440 (Fed. Cir. 1991).

Inequitable conduct also requires definite proof of culpable intent. "[M]ateriality does not presume intent, which is a separate and essential component of inequitable conduct." *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1002-03 (Fed. Cir. 2006) (intent wrongly inferred from failure to provide full translation of reference). Intent should not be too easily inferred from circumstance, particularly when there is a reasonable explanation for what happened. *Northern Telecom, Inc. v. Datapoint Corp.,* 908 F.2d 931, 939 (Fed. Cir. 1990) (noting "the ease with which a relatively routine act" can be portrayed as misleading). Accordingly, "[i]ntent to deceive can not be inferred solely from the fact that information was not disclosed." *Hebert v. Lisle Corp.*, 99 F.3d 1109, 1116 (Fed. Cir. 1996). A court may not infer deceit, akin to a fraud, "simply from the decision to withhold a reference where the reasons given for the withholding are plausible." *Dayco Prods., Inc.*, 329 F.3d at 1367. Likewise, gross negligence is not inequitable; the "involved conduct,

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[5] Under an older standard, information was material when there was a substantial likelihood that a reasonable examiner would consider it important in deciding patentability. *Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1363 (Fed. Cir. 2003); *see* 37 C.F.R. § 1.56 (1991). The Federal Circuit still relies on the older rule, tempered by what the new rule indicates is important. *Digital Control*, 437 F.3d at 1316.

viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive." *Kingsdown Med. Consultants, Ltd. v. Hollister Inc.*, 863 F.2d 867, 876 (Fed. Cir. 1988) (*en banc*).

If the court finds threshold levels of materiality and intent, it still must carefully balance them, for example: 'the less material the information, the greater the proof [of intent] must be." *Purdue Pharma*, 438 F.3d at 1129; *see also CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1343 (Fed. Cir. 2003). This is an equitable determination: was the applicant's conduct so egregious and culpable that the patent should not be enforced. *Kingsdown*, 863 F.2d at 875, 877.

Here, Novozymes did not cite the Machius '95 reference; but this was not inequitable. At most, Machius was cumulative of Suzuki and Bisgärd-Frantzen, already before the Examiner. **A6102:2-25**; **A6530:3-18**. The Borchert Declaration was not inequitable either. It appropriately reported a fair experiment showing the relative improvement of the claimed alpha-amylase variants compared to the Suzuki variants, and to their wild-type parent enzymes. **A6549:23-A6550:15** Moreover, there is evidence of good faith; and no evidence of intent to deceive the PTO. *Kingsdown*, 863 F.2d at 876.

(a) The Machius '95 Reference

Novozymes was aware of the Machius reference. **A5012:8-12; A5657:11-14**. Mr. Garbell and Dr. Borchert carefully considered Machius when it was raised in an *inter partes* PTO interference involving a different patent. They did not believe Machius was material. **TE-524, A8915-17; A5599:11-24; A5632:8-5638:23; A5662:8-12; A5672:11-5674:14**. It did not establish unpatentability or contradict any position taken by Novozymes. 37 C.F.R. §1.56(b). Indeed, the uncertain Machius structure was particularly off-base, because the '031 claims concern amino acid changes (like Suzuki), and not a crystal structure *per se*, as in the interference. **A5657:15-19**. Even there, serious problems with Machius were identified by Dr. Borchert. **TE-524, A8915-19**. Here, Machius is less relevant than Suzuki, at most is cumulative, and did not have to be given to the PTO. **A5641:2-6, A5660:12-18**.

Mr. Garbell did not think Machius added anything to what the Examiner already had before her. **A5672:14-17; A5673:5-10; A5673:19-21; A5675:9-20** Based on his review from the interference, he did not find a reason to consult further with Dr. Borchert, nor did Dr. Borchert feel differently. **A5673:11-5674:14**. Notably, Mr. Garbell was aware of and consistently strove to meet his duty of disclosure to the PTO. **A5676:19-5678:3**. He did not experience any doubt about the immateriality of Machius or whether it should be cited. ***Id***. Dr. Borchert read Machius shortly after it was published and during the interference. **A5591:22-5592:5**. He had many conversations about Machius with Mr. Garbell. **A5671:16-5672:2; A5676:4-8**. With help from Mr. Garbell, he prepared the interference declaration (**TE-524**), which discusses Machius. **A5601:10-5603:3**. Still, and for good reason, neither of them saw Machius as material to the '031 prosecution. **A5645:21-5646:4; A5673:11-A5674:14**.

The interference provides contemporaneous evidence of good faith. *See* **TE-524; A8931; TE-508; A-8862**. Dr. Borchert and Mr. Garbell believed that Machius was fatally flawed, *e.g.*, it did not provide the coordinates necessary for a reliable structure, and it referred to a calcium-depleted, cleaved protein, which was of very limited use. **TE-524; A-8915-17**. Given these views, the different claims in the interference, and the '031 disclosure of Suzuki and Bisgärd-Frantzen, there is a reasonable explanation for not citing Machius. There is no clear and convincing deceptive intent, and no inequitable conduct.

Objectively, Machius is cumulative prior art at best. It could not have been "inequitable" to forego citing it. *FMC Corp. v. Manitowoc Co.*, 835 F.2d 1411, 1415 (Fed. Cir. 1987). Machius discusses Suzuki, but does nothing more to help a protein engineer make and use the variants Suzuki already disclosed, nor variants which might be extrapolated from Suzuki. **A6517:13-6523:4.** Machius is based on a distorted X-ray model and disputes the very theories it presents on thermostability. ***Id.***; **A5635:15-20; A5716:11-5718:23; A5724:25-5725:8; A5725:23-5727:12; A5729:23-5731:21**. Machius adds uncertainty; it does not clarify any questions or solve any problems. In fact, Machius is evidence that designing better proteins remained unpredictable, could

not use speculative theories, relied on trial and error, and did not affect Suzuki's empirical results. **A5632:8-5638:23; A5662:8-12; A5672:11-5674:14; A6115:16-6118:11; A6503:24-6505:14; A6506:18-6507:4; A6509:2-6510:6; A6514:10-25; A6515:16-6526:14; A6527:13-6530:18;** *see also* §II(D)(2), above. Machius was, at best, cumulative. Not citing it to the PTO cannot constitute inequitable conduct. *Eli Lilly* at 1574-75. The record cannot support a finding of culpable intent either, and a weighing of all the evidence precludes a judgment of unenforceability. **A5662:8-12; A5673:5-11; A5676:19-5677:4.**

(b) The Borchert Declaration

Novozymes gave experimental data to the PTO in a Declaration of Torben Borchert, dated September 7, 2004. **TE-508.** The 179,180 BSG deletion was compared with the closest prior art: Suzuki's 176,177 BAN deletion. ***Id.*** **at A8857-8, ¶3,4; A5660:17-19; A5585:10-11; A5596:2-9.** Thermal inactivation tests showed that the improved thermostability for BSG was unpredictably high compared to the BAN. ***Id.*** at **A8861-2, ¶9**; *see also* §II(D)(1), above.

Dr. Borchert set out to do a fair and reliable comparison of the effect this deletion has on thermostability. **A5640:19-5641:1; A6092:11-14.** He designed the experiment and drafted the Declaration, with help from Mr. Garbell. They discussed that good (desired) and bad (undesired) results must be presented to the PTO. **A5662:13-18; A5665:10-19; A5666:2-11; A5677:5-21.** The work was done in Denmark by Dr. Borchert and Novozymes technicians. **A5586:10-14; A5641:20-5642:3, A6073:10-6074:5.** In fact, a few raw data points were not used by Dr. Borchert or his technician, for a very good reason: they were scientifically unreliable. **A5614:25-5617:19; A5643:2-5645:17; A6546:1-6548:5; A6549:7-20.**

Dr. Borchert's work was well-designed, properly conducted, and honestly reported. He used the same protocol as Genencor in its patent applications, for the same BSG variants. **TE-202, A8532.25 (Example 3); A6538:24-6539:4; A6539:13-6541:3.** The experiment used an industrially-relevant low calcium concentration (0.1 mM) (**TE-508, A8858-59, ¶5**), as in the patent (**TE-100 at 30:62-67**). Reduced calcium was a particular goal of the invention. ***Id.*** **at 1:21-24,**

2:61-66, 4:7-12; A6092:15-25; **A6114:18-20**; **A6535:20-6536:11**. The experiment was done at 80°C (**TE-508, A8858-59, ¶5**), which was "a fair temperature to choose" (**A6536:-25**), especially for an industrial enzyme (**A6536:12-25**). Tests showed that the BAN and BSG enzymes could be evenly compared at this temperature. **A6076:21-6077:4**; **A6094:8-A6096:6.** The test buffer was not pre-heated, but this was reasonable with the thin test-tubes and pre-heated equipment that was used. **A6078:12-15**; **A6075:5-14; A6538:17-21; A6541:12-20**. Additional work showed that "ramp up time" was not a real factor; a pre-heated buffer would not have materially changed the outcome. **A6544:3-11**; **A6545:22-25; TE-218**. Genencor does not use a pre-heated buffer either, for the same tests on the same enzymes. **TE-202**, **A8532.25** (Example 3)**; A6538:24-6541:3**. The data analysis was reliable, including log plots and regression analysis to determine half-life. These are standard methods, and are used the same way by Genencor. **A6542:7-6543:5; TE-202**.

Each sample was read twice. **A5808:10-16**. Two BSG wild-type readings at 20 and 40 minutes were questioned and not used, but the two parallel readings were fine and were used. **A5770:15-5771:6**. One BSG variant sample at 2881 minutes had evaporated, and both of its readings could not be used. **A6079:5-14**; **A5643:17-24; A6079:5-9**; **A6549:7-20**; **A6020:14-24**. Another BSG variant sample at 2940 minutes gave two widely different readings, one of which showed more enzyme activity after two days of heat than at the start of the experiment (>100%). This was highly questionable, and those two readings could not be used. **A5643:25-5644:2**; **A5809:22-A5810:5**; **A5645:8-17; A6022:11-13**.

These were honest and reasonable judgments of the kind made by scientists every day. **A6549:1-20.** The experiment showed what was really going on, and the questioned readings would not change the overall result. **A6550:3-15**. The thermostability of the BSG variant is unpredictably high vs. its wild-type, compared to Suzuki's BAN variant vs. its wild-type. **A6550:16-22**.

Dr. Borchert's experiments and the results in the Declaration are trustworthy, and show substantial and surprising improvements in thermostability for the claimed alpha-amylase variants. The Declaration disclosed the conditions of the comparative tests that were done and fairly

Dr. Borchert's experiments and the results in the Declaration are trustworthy, and show substantial and surprising improvements in thermostability for the claimed alpha-amylase variants. The Declaration disclosed the conditions of the comparative tests that were done and fairly reported the results. Novozymes did not withhold or misrepresent material information. There was no intent to mislead the PTO. There was no inequitable conduct. There is no evidence of culpability so clear and convincing that the '031 patent should be struck down. *Kingsdown*, 863 F.2d at 876.

III. CONCLUSION

For all of the reasons given, the Court should enter judgment: (1) holding that the '031 patent is infringed; (2) holding that the '031 patent is valid and enforceable; and (3) permanently enjoining the Defendants from any manufacture, use, offer, sale or importation in the United States, of Spezyme Ethyl, or any other product that infringes the '031 patent.

Respectfully submitted,

Dated: April 21, 2006

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CERTIFICATE OF SERVICE

I, Andrew A. Lundgren, hereby certify that on April 21, 2006, I caused to be electronically filed a true and correct copy of the foregoing document with the Clerk of the Court using CM/ECF, which will send notification that such filing is available for viewing and downloading to the following counsel of record:

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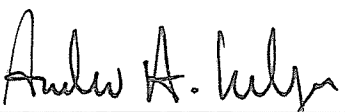

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